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REVIEW ON MICROFLUIDIC PAPER-BASED ANALYTICAL DEVICES TOWARDS COMMERCIALISATION

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Abstract

Paper-based analytical devices introduce an innovative platform technology for fluid handling and analysis, with wide range of applications, promoting low cost, ease of fabrication/operation and equipment independence. This review gives a general overview on the fabrication techniques reported to date, revealing and discussing their weak points as well as the newest approaches in order to overtake current mass production limitations and therefore commercialisation. Moreover, this review aims especially to highlight novel technologies appearing in literature for the effective handling and controlling of fluids. The lack of flow control is the main problem of paper-based analytical devices, which generates obstacles for marketing and slows down the transition of paper devices from the laboratory into the consumers' hands.

1. Introduction

Microfluidics is very well established in academia and it is rapidly gaining positions in industry mainly for the development of new methodologies and new products for life sciences. There have been significant developments in the microfluidics field since the first real microfluidic technology was developed in 1979 by S. C. Terry *et al.*,[1] nevertheless, the amount of commercial products based on microfluidics is, with few exceptions, low. In particular, "Lab on a paper" or "paper-based microfluidics" has become an expanding research field since 2007,[2] providing a way to deliver, simple and cheap microfluidic devices easily manageable by the end-user.[3]

Paper is now considered an attractive and promising substrate material for microfluidic applications not only due to its extremely low cost and ubiquity but also due to its mechanical properties comprising flexibility, lightness, and low thickness. Paper is produced from a dilute aqueous suspension of cellulose fibres that are drained through a sieve, pressed and dried, to yield a sheet formed by a network of randomly interwoven fibres.[4] Its fibrous and porous structure provides; 1) capillary action, leading to the transportation of the liquids without a need of an external force, 2) absorbency, enabling the storage of the reagents inside the paper, 3) air permeability, removing the air bubble problem, 4) a network structure, enabling the filtration of the sample and 5) a high surface to volume ratio, increasing the number of possible reagents immobilised, causing a considerable fall in the time for the analysis. Due to its natural, high biocompatibility (which has a significant meaning for the samples), biodegradability, disposability and chemical and biological inertness, is particularly important for the immobilisation of reagents (Figure 1).[3,5-13]

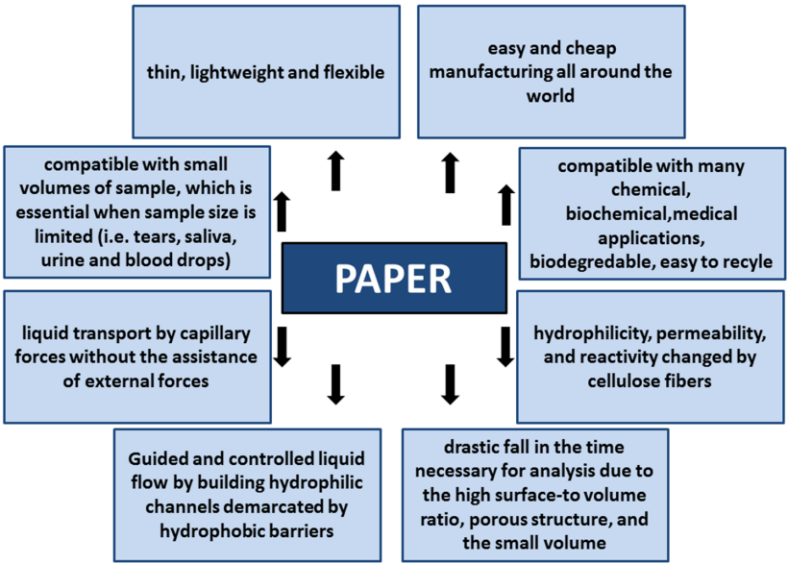


Figure 1. Key points of paper for microfluidic paper-based analytical devices (µPADs).

µPADs, are novel analytical tools which are fabricated with paper material capable of analysing complex and small amounts of biochemical samples (10^{-9} to 10^{-18} L) , within one analytical run, where microfluidic manipulations like transportation, sorting, mixing or separation are available.[14] Considering the amazing properties of paper material, µPADs represent an innovative platform technology for fluid handling and analysis, with wide range of applications, featuring low cost, ease of fabrication/operation and equipment independence.

Here, we aim not only to have a general overlook on the fabrication techniques, the technologies and capabilities of paper-based microfluidic devices reported to date, but also reveal the weak points of these devices and the newest approaches followed by researchers in this area to overtake those limitations. In this review we especially wanted to highlight the novel technologies introduced in paper microfluidics as solutions for the effective handling and controlling of fluids, since lack of flow control is the main problem of µPADs, which generates obstacles for marketing and slows down their transition from the laboratory into the consumers' hands.

2. Device Fabrication

In 1949, Müller and Clegg produced a paraffin-patterned paper that can be named as the first time fabrication of a fluidic channel on paper, as well as the first paper-based assay.[15] The real introduction of paper-based microfluidics to the scientific world was attributed to Whitesides' Group at Harvard University, whose first device was a protein-glucose assay created by a lithography method in paper.[16] Since then, a large variety of fabrication techniques have been developed. The fundamental methods for fabrication reported up to now are compared in Table 1 considering their compatibility for mass production.

Table 1. Comparison of μPAD fabrication methods.

Fabrication Technique	**Equipment**	**Consumables**	**Advantages**	**Drawbacks**	**Refs.**
Cutting	Computer, X–Y plotter or CO_2 laser.	None	Sharp defined features	Requires expensive equipment; waste of raw material; yields low-mechanical stability; need a cover tape for preventing pollution and increasing	[17-24]

				robustness of the device.	
Photo-litography	Litho-graphy equipment, UV lamp printer, hot plate or laser equipment without mask	SU8-2010 photoresist, Octadecyl-trichlorosilane (OTS), Ultraviolet resin, SU8 2150 negative photoresist, TiO_2	High resolution of microfluidic channels; sharp barriers	Requires expensive equipment; complex steps; expensive reagents	[25-36]
Polydimethyl-siloxane (PDMS) printing	Desktop plotter	PDMS	Cheap patterning agent (PDMS); flexible devices	Inconsistent control over hydrophobic barrier formation; low resolution; requires a curing step; cannot be readily applied to high throughput production.	[37]

Ink-jet etching	Modified ink-jet printer	Polystyrene	Low cost; requires only a single printing apparatus to create microfluidic channels and to print bio/chemical sensing reagents	Requires multiple printing steps for the creation of the microfluidic channels; the printing apparatus must be customised; complex number of steps; not suitable for mass fabrication	[38,39]
Wax dipping	Customised masks, heating unit	Solid wax	Very cheap and easy method	Inconsistent between batches due to the variation in dipping; not good for mass production	[40,41]

Flexography printing	Customiced printing equipment	Polystyrene	Allows direct roll-to-roll production in pre-existing printing machinery; avoids heat treatment of the printed patterns	High cost; complex reagents and templates; surface requires frequent cleaning to avoid contamination; printing quality depends on smoothness of paper surface; requires different printing plates	[42]
Screen printing	Customised masks	Solid wax, polystyrene	Low cost; simple fabrication steps	Low resolution of microfluidic channels; rough barriers; requires different printing screens for creating different patterns; not good for mass production	[43,44]

Wax printing	Wax printer, hot plate	Solid wax	Produces massive devices with a simple and fast (5-10 min) fabrication process	Poor availability in resource limited settings; low resolution; requires an extra heating step after wax deposition	[45-51]
Stamping	PDMS stamp or stainless steel stamp	Commercial ink or paraffin	Low cost, simple	Inconsistent process; low resolution; preheating of the stamp, and oxidisation of the paper are needed in the case of paraffin stamping with a metal stamp	[52-54]

Plasma treatment	Customise masks, hot plate or oven, vacuum plasma reactor	Alkenyl ketene Dimer (AKD); Fluorocarbon; Poly(hydroxybutyrate) (PHB)	Uses very cheap patterning agent AKD or fluorocarbon; dramatically reduces the cost of materials	High cost; requires different masks or glass slides for creating the microfluidic patterns on paper	[55-57]
Ink-jet printing	Modified ink-jet printer	AKD; Methylsilsesquioxane (MSQ); UV curable acrylate; special ink	High resolution; requires only a desktop printer to produce devices and to print sensing reagents	Requires modified ink-jet printers; different ink compositions for each printing; mostly requires an extra heating step after deposition	[58-62]
Vapor phase deposition	Deposition chamber	Poly(chloro-p-xylene) Poly(1H,2H,2H-	Simple steps; complex patterns can be accomplished	High cost equipment	[63-65]

		perfluorodecyl acrylate)			
Wet etching	Paper mask, glass slides	Trimethoxyoctadeculsilane (TMOS)	Simple and fast	High cost need a paper mask with specific designs	[66]
Hand-held corona treatment	hand-held corona generator, plastic mask	OTS	Low cost; simple fabrication steps	Heating process is needed	[67]

Table 2 presents a schematic overview of the most used μPAD fabrication methods. Fabrication of paper-based microfluidic devices can be divided into two general categories: two-dimensional shaping/cutting of paper and patterning hydrophilic/hydrophobic contrasts on paper.

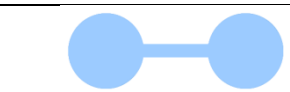
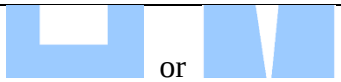
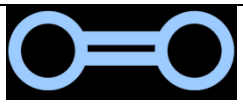
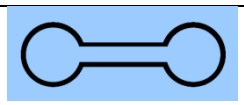
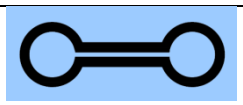
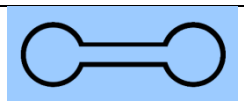
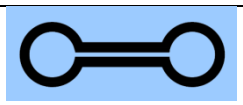
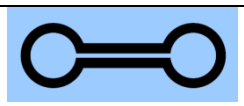
In the cutting category, the paper channels are generally obtained by cutting the paper with a cutter plotter capable of controlling the X-Y axis or with a CO_2 laser cutting apparatus. Then, in most cases, the cut channels are covered with a sticky tape as a backing to give certain microfluidic like structure and higher strength of the full device.[3] The main drawbacks of the cutting method for mass production are the fabrication costs, since requires a specialised type of equipment sometimes not economically viable, and the energy power limitations in limited resources areas or in field. On the other hand, achieving a hydrophilic pattern on paper with hydrophobic borders would define the fluidic channel on a μPAD. In order to obtain a hydrophilic/hydrophobic contrast on paper there are several patterning techniques which are

divided into three subcategories, depending on the binding states of hydrophobic agents to paper: 1) Physical blocking of the pores, 2) Physical deposition of a hydrophobising agent on the paper fibre surfaces, 3) Chemical modification of the paper fibre surface.

Physical blocking (using agents such photoresist and PDMS) and physical deposition on the fibre surface (using polystyrene, wax or commercial ink) do not involve any chemical reaction between the agents and the paper fibres. These hydrophobic agents change the wetting property of paper by filling the paper pores or adsorb on the fibre surface.[68]

The photolithography patterning is based on entire hydrophobisation, followed by selective dehydrophobisation of the paper. Whitesides´ group introduced this method by patterning chromatography paper with SU-8 2010 photoresist.[16,28] With this technique, chemical-resistant solid barriers can be formed in high resolution and very small dimensions. Nevertheless it is not an ideal method for mass production due to high cost of the equipment needed, the necessity of multiple steps to get the device and the bending vulnerability of the final devices that could easily crack. In order to reduce the cost and increase the flexibility, in their later works, the same group used an epoxy negative photoresist,[29] and SC (cyclized poly(isoprene) derivative) photoresist,[30] and introduced UV lamp and hotplate to eliminate the use of lithography machine.[29] Moreover, a laser directing method was introduced in order to avoid the use of photomasks.[31-32,69] He *et al.*[33] presented a photolitographic fabrication method by means of coupling of hydrophobic silane, OTS, to paper fibres followed by deep UV-lithography. It avoided the adoption of high cost photo resists.

Table 2: Comparison of the different fabrication protocols

Fabrication Method	Step 1		Step2	
Cutting	Shaping by cutting		---------	
	Surface area			
	Cross-section	 or		
Photolitography	Applying photoresist		UV light + photomask	
	Surface area		Surface area	
	Cross-section		Cross-section	
Ink-jet (AKD) printing	Printing		Curing	
	Surface area		Surface area	
	Cross-section		Cross-section	
Wax printing	Printing		Heating	
	Surface area		Surfare area	
	Cross-section		Cross-section	
Ink Stamping	Stamping		----------	
	Surface area			
	Cross-section			

In order to decrease the time for photomask fabrication and the cost, He *et al.*[34] generated a dynamic photomask LCD, digital micromirror device. They used a desktop stereolithography 3D

printer and an ultraviolet resin for μPAD fabrication, the so called, dynamic mask photo curing (DMPC). Songok *et al.*[35] reported a two-step patterning process creating hydrophobic surfaces with a TiO_2 nanoparticle coating by using a high-speed, roll-to-roll liquid flame spray technique followed by UV irradiation through a photomask in order to form the hydrophilic pattern. The use of a roll-to-roll technique was very positive, but the cost of the liquid flame spray reduced its possible commercial use, since increased the final product price. Nevertheless, the recent improvements on photolithography patterning could decrease the complexity of this type of fabrication methods.

Wax-based fabrication techniques are low-cost methods based on selective hydrophobisation using non-toxic patterning reagents. The recent wax impregnation technology "wax printing" was introduced by Lu *et al.*[45] in 2009. Despite being a two-step method including paper printing and heating, it is suitable for mass production, since wax printers are commercially available and inexpensive to operate, being the principal μPAD fabrication method used in literature at the moment.[69,70] The drawback of wax printing is the melting of the wax during long term-storage at ambient air conditions, the possible cross contamination of the samples with the wax and the modification of device dimensions (channels) over time.[3]

Recently, the ink stamping method described by Curto *et al.*[52] and the double side stamping method developed by Akyazi *et al.*[54] became alternatives to conventional wax printing since are fast and cheap prototyping techniques based on forming hydrophobic ink channels on paper using a PDMS stamp and indelible inks. They could be considered economical fabrication methods but have a main drawback: they are manual processes, so the reproducibility from device to device is low. Nevertheless authors suggested that the processes could be easily scalable for mass production and integrated into roll-to-roll instrumentation.

Garcia *et al.*[53] introduced another economical stamping technique where the design of the microfluidic structure was patterned in a lightweight and portable stainless steel stamp for rapid prototyping of µPADs, using paraffin over a chemically modified paper substrate. Preheating of the stamp and oxidisation of the paper surface were additional steps that could be considered drawbacks. In general, stamping methods are ideal for easy and portable fabrication of µPADs, but they are considered weak methods for mass production. Nevertheless, it needs to be considered that they are good device candidates to be used in field and under resource limited settings.

Nuchtavorn *et al*.[71] presented a novel fabrication method using inks (commercial ink and in-house formulated aqueous inks) to obtain hydrophobic patterns; employing a desktop digital craft plotter/cutter integrated with technical drawing pens. With this method it was possible to obtain a variety of designs in a highly flexible manner, rapidly and offering a low cost fabrication protocol. Technical drawing pens provided flexibility in the used of different type of inks. Therefore, it is another technique convenient for mass production and comparable with the wax printing method.

On the other hand, chemical modification paper surfaces is based on the use of cellulose reactive agents (commonly, AKD) which typically react with the "-OH" groups of cellulose, leading to the hydrophobicity of the cellulose fibres.[68] Hydrophobic AKD channels were typically formed by plasma treatment[55-57] and lately by ink-jet printing methods.[58,59] In the case of AKD, the printing process is followed by a curing step.[58] In contrast to laser treatment, printing methods have a high potential for mass production.[3,59,69] Ink-jet printing has evolved over time thanks to groups searching for alternatives to AKD. For instance, Wang *et al.*[60] compared hydrophobic sol-gel derived methylsilsesquioxane (MSQ) with wax and AKD in µPADs fabricated by ink-jet printing. This team found out that, while all three barriers performed well with water, only the MSQ barrier was not breached by aggressive cell lysing solutions or surfactant solutions,

demonstrating that MSQ is more convenient material for fabricating µPADs. Moreover, Maejima *et al*.[61] adopted a hydrophobic UV curable acrylate composition composed of non-volatile and non-flammable compounds to replace AKD in the ink-jet printing method. Finally, Xu *et al*.[62] developed a rapid fabrication method ideal for mass µPAD production by double-sided printing with permanent marker inks onto the filter paper with the ink-jet printer.

Duman *et al*.[72] developed a fabrication technique which is a combination of ink-jet printing and microwave irradiation. This resulted in the low cost device fabrication method without using any photoresist agent and eliminating any curing steps, cutting and heating. Considering the development of these type of processes, ink-jet printing can be considered as a promising method for mass fabrication of µPAD. These printing methods provide good control on the deposition of ink, picoliter to nanoliter volumes, and on the generation of finely tuneable patterns with high resolution, and potential for roll-to-roll processing.[70] Nevertheless, ink formulation depends on the ink-jet printing, which demands different ink compositions to achieve a clog-free, consistent pattern on a paper substrate. Moreover, due to the dot-by-dot deposition of ink droplets, the process is slower than other printing systems where the entire pattern is transferred to the substrate in one step. Therefore, a major drawback comes in terms of speed.[73]

µPAD fabrication by chemical vapour-deposition of polymers to form hydrophobic barriers was reported by several groups. Nevertheless, the chemical vapour deposition chamber requires expensive equipment, not available or suitable in many laboratories or industries.[63-65]

Cai *et al*.[66,74] introduced another chemical fabrication method for µPADs free of any expensive equipment and metal masks: silanisation of filter cellulose using a paper mask with specific patterns. This achieved the first patterned filter paper using a TMOS solution. Other silane barriers such as tetrakis-(dimethylsiloxy)silane and 1,3-dimethyltetramethoxysilane were used by

Rajendra and co-workers[75] to generate barriers too, showing resistance to aqueous, organic, and surfactant solutions. Moreover, Jiang *et al.*[67] showed that hydrophobic paper generated by treatment OTS and a hand-held corona generator was successfully used to fabricate operative μPADs; this is a portable and ideal technique to be used in resource limited settings.

Other methods such as PDMS patterning,[36] flexographic printing,[42] ink-jet etching,[38-39] screen printing,[43-44] printed circuit technology,[76] subtractive laser treatment,[20] have also been considered by researchers in order to form a hydrophilic/hydrophobic contrast. Nevertheless they also failed for being ideal fabrication methods for mass manufacture due to their multistep processes and high fabrication/equipment costs.[3]

The three dimensional (3D) microfluidic paper-based technology, introduced by Whitesides' group,[28] is of great interest due to the advantages it offers for certain applications in life sciences (health & environmental), Figure 2. These platforms grant fluid movement in three dimensions, which increases distribution times and decreases the necessary sample volume for the assay. This configuration enables de fabrication of multi-step assays or multiple assays in the same footprint of a 2D device. The principle of 3D device fabrication is assembling the individual patterned and reagent-deposited paper sheets into the final device by preserving the contact between the hydrophilic parts of each layer. It is remarkable the 3D fabrication technique, which uses one single paper and where the paper is folded by origami technique and assembled by external clumps,[18] by double and single sided adhesive tapes,[77] or by patterned spray adhesives.[78] Since then, the origami technique has been adopted by many 3D devices for measuring analytes.[79-83]

Individual paper layers have been combined by patterned double-sided adhesive tapes,[84] by hydrophilic uniform spray adhesives,[85] or staples.[86] It is remarkable the work from Li *et al.*[49] that presented the possibility of obtaining 3D microfluidic channels inside a single paper

layer by wax-printing based technique where the wax is applied through both sides of the paper. Similar to this work, Jeong and co-workers,[50] fabricated another single layer 3D device by using double-sided wax printing to generate the microfluidic network. This double-sided printing method has shown promises for mass production due to its rapid fabrication time. Finally, Camplisson *et al*.[51] developed a 3D μPAD by using a two-layer configuration. It was found that the wicking rate of the two-layers system was significantly higher than that in one-layer devices. Moreover, Thuo *et al*.[87] obtained 3D microfluidic paper channels which behave like open channels by the embossing and cut-and stock method using both one single paper layer and two paper layers.

3D printers have been reported recently contributing to the fabrication of μPADs.[34,36,70] Asano *et al*.[36] used a photomask printed with a 3D printer for the fabrication of hydrophilic and hydrophobic zones on paper by UV photolithography. They used OTS/*n*-hexane solution as the hydrophobising agent. The fabrication method has high stability, resolution and precision for hydrophilic channel and hydrophobic barriers reducing fabrication times. Pearce *et al*.[88] modified 3D printers to be used as wax printers, generating complex 3D geometries at low cost.

The ideal fabrication technique can be a 2D or 3D method depending on the application. The final aim is to obtain low cost-high performance assays suitable for mass production; therefore choosing the appropriate fabrication method is only possible by considering the cost of these fabrication techniques, the equipment available as well as the performance of the fabricated devices. At present, ink-jet printing and wax printing are the most promising techniques due to their ease and rapid fabrication protocols and the low patterning agent costs, which enable mass production. In the other hand, techniques like ink stamping and hand-held corona treatment could be ideal for resource limited settings, where the reproducibility on the device design is not a major problem.

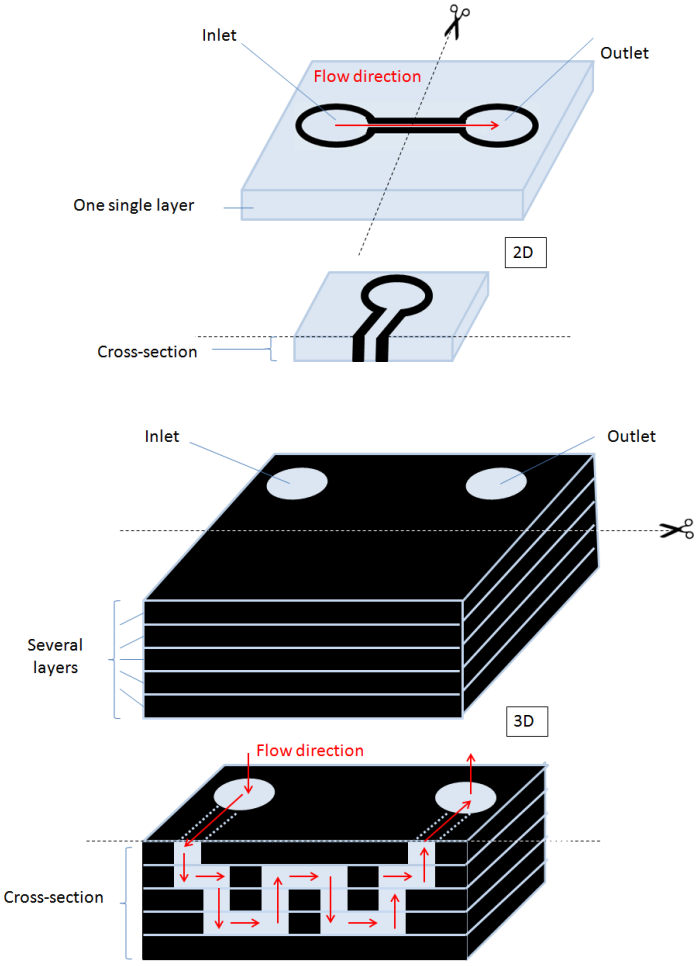


Figure 2: Schemes of 2D and 3D fabricated device.

3. Fluid Control and Fluid handling in µPADs

Paper-based microfluidic analytical devices demand several capabilities in addition to the mere platform for driving the assay. These capabilities should respond to basic requirements such as ensuring a precise sample volume, a fixed assay time, reagents storage, a low cost high performance reader and a low or even no power supply for the reader, among others.[3] Moreover µPADs also aim to increase the sensitivity and the capacity of the device. In an ideal paper-based microfluidic device, all capabilities should be directly integrated into the device, increasing usability, enabling Point of Care (POC) while also being compatible with the typical features (lightweight, low cost, easy-operability, …) of the device.[3]

Cellulose fibres are the driving force for fluid wicking by capillarity motion in paper. Thanks to capillary forces, there is no requirement for the external pumps to provide fluid transport inside the paper unlike the traditional microfluidic platforms. Nevertheless isotropic wicking behaviour of paper and its capability of transporting fluid in any surface direction area becomes a drawback.[47] In commercially available paper, accurate fluid flow control is challenging and most of the times complicated, thanks to the influence of the type of fibres used, the paper porosity, as well as the presence of chemical additives in the-paper.[89] Lack of fluid control on paper is at this moment the main dragging force for researchers when looking for new applications of µPADs and was just on 2016, when Jeong *et al.*[90] reviewed the methods available for flow control in µPADs.

The different ways of obtaining patterned barriers by hydrophobic materials, as mentioned in the previous section, can be as well used for fluid control in µPADs. Nevertheless, they have never been proved to be sufficient to assure fluidic control in the device. Flow control is essential for applications that involve reagent /sample additions controlled by time, sequential injections/dilutions,[70] consequently, switches, valves and fluidic timers are developed as new mechanisms to control flow inside the µPADs hydrophobic barriers.

Li *et al.*[55] for instance, developed the first microfluidic switch in a µPAD, which allows or restricts capillary flow by applying pressure manually, by cutting a channel into two parts and then separating the channels, Figure 3. It can be considered as a simple and effective method for selective dosing and fluid control. Later, Whitesides' group built a similar but more complex valve mechanism in a 3D µPAD, which delivers fluid flow by closing the gap between two vertically aligned fluidic channels and allowing wicking continuously by applying pressure, Figure 4. This

system is basically beneficial in applications where the sample volume is a limiting factor. Moreover, the vertical channels were formed by complex fabrication techniques and were connected by adhesive tapes or glue where alignment was a problem. [91]

Shin *et al.*[92] reported a flow control method by pressurising a specific region in the paper-based channel for programmed sample delivery. As a result, in the pressed region, permeability and fluid resistance is decreased and increased, respectively, creating fluid delays. They proved that flow rate decreased in accordance with the applied pressure. Moreover, this method demonstrated flow rate control for sequential delivery of multiple fluid samples in a polypropylene sheet-based device that performs a multi-step colorimetric immunoassay.

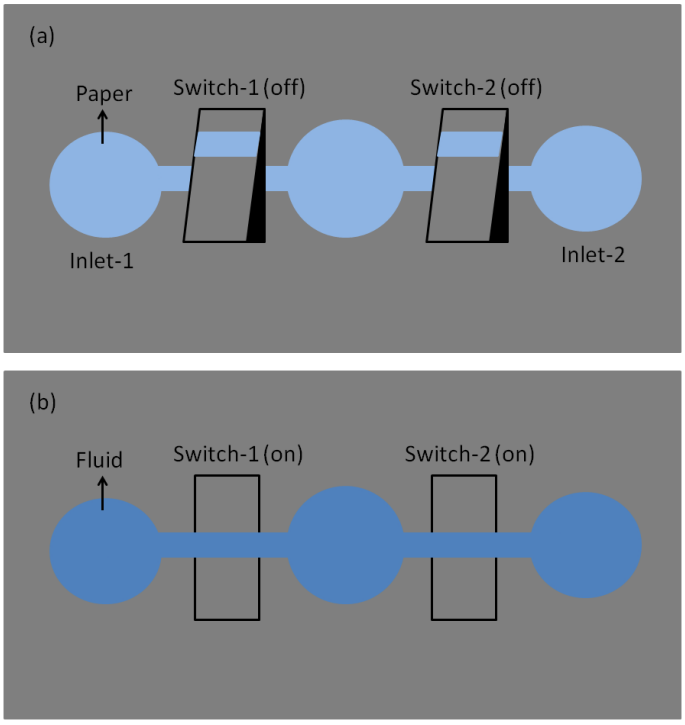


Figure 3: Scheme of a paper-based microfluidic device with two pressure sensitive switches. (a) Switches are in the "off" position. (b) Switches are "on", and fluid can flow all over the paper channel.[55]

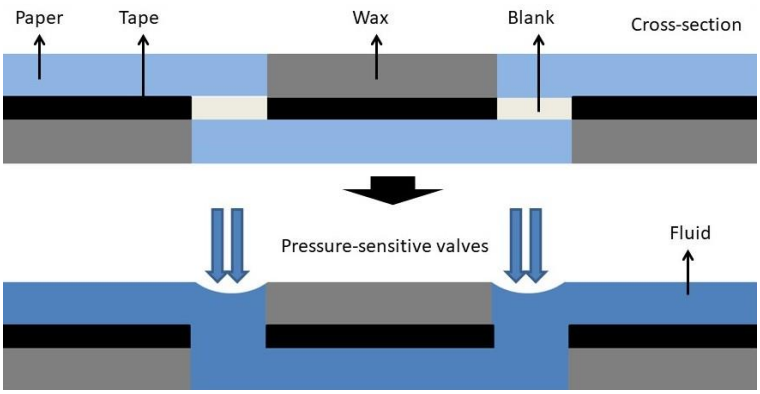


Figure 4: Pressure-sensitive valves on a 3D fully assembled paper device, before (top) and after (bottom) valve actuation. [91]

Lutz *et al.*[93] developed 2D microfluidic networks with programmable fluidic disconnects to obtain paper-based valves. The 2D microfluidic network has legs with different lengths, and these legs are dipped in the fluid reservoir. The legs disconnect in their order of length in a programmable schedule sequence when fluid level drops. Despite of being simple, easy and efficient for controlling the sequence of fluid delivery, this method was not enough to control the exact timing of fluid delivery when more complex fluidics are needed. Fu and co-workers [94] showed that in a multi-step 2D paper network the arrival time of multiple fluids into the sensing zone as well as the transport time of the fluid front can be altered and controlled by modifying the length or width of the microfluidic channels, which form the traveling path of the fluid (from the inlet to the sensing zone). In their later work, they demonstrated a two-dimensional paper network working with the same principle for automatic sandwich format immunoassay including signal-amplification for the malaria protein Pf HRP2. Multiple inlets connected to the detection zone allowed sequential arrival of the reagents to the detection zone and enabled high performance for automatic multistep operations. [2] Apilux and his team[95] introduced the printed baffle design to increase the length of the paper-based channels that enable time delays of sequential reagent

flows to the detection region-in a sandwich-type enzyme-linked immunosorbent assay (ELISA) on paper microfluidics. Fu *et al.*[94] introduced another concept; dissolvable barriers used as flow modulators, producing a delay in the fluid flow in a specific segment of the µPAD. Fluid wetted the barrier and decreased the flow speed during dissolution, then moved freely to its final destination. In this particular case the fact of dissolving a material into the sample could generate interferences during analysis.

Recently, Houghtaling *et al.*[96] demonstrated an innovative dissolvable bridge structure as shut-off valve for autonomous delivery of multiple volumes, from the same source to different pathways in a paper network device, Figure 5. The system has the capacity to carry volumes ranging from 10 to 80 µL by adjusting several parameters such as geometry and composition of materials in the bridge structure. Moreover it enables simple user loading with the potential of generating more efficient and sophisticated assays.

Another fluid control method introduced by Toley *et al.*[97] achieves flow delay through the modification of the fluid flow by a-tuneable absorbent pad-based shunt located on top of the main channel, Figure 6a. Reproducible flow delays varying from 3 min to around 20 min can be generated with this novel ¨shunt¨ valving mechanism by altering the parameters like the dimensions of the shunt material. Moreover, the same absorbent shunt is able to transfer higher amounts of fluid volumes, which is an important advantage. They have been used to perform sequential delivery in µPAD designed for the detection of a malaria antigen, proving their POC compatibility. This type of technology has implications for the fabrication of autonomous, POC µPADs. Nevertheless, their utility, under varying environmental conditions, *i.e.* high humidity levels and temperatures have not been demonstrated yet.

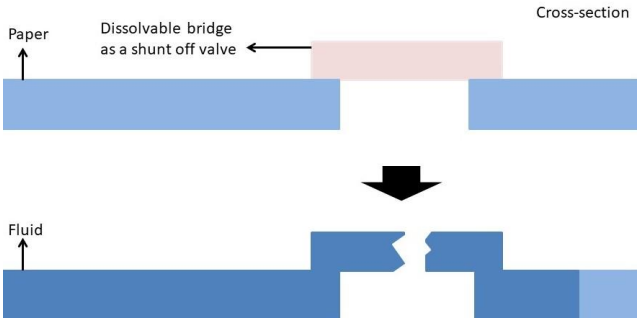


Figure 5: Paper device with dissolvable bridge. The bridge material dissolves to a permanent shut-off state after passing a well-defined volume of fluid from the feeder material to the delivery material.[96]

The same year, Lutz and his team developed dissolvable sugar fluidic restrictors to create flow delays and so, programming multistep assays for paper diagnostics. This basic concept was used to perform a signal-amplified sandwich POC immunoassay for diagnostic of a biomarker for malaria, Figure 6b.[98]

Soon later, Jahanshahi-Anbuhi *et al.*[99] introduced a regulated time flow-shut off valve system fabricated with pullulan, a rapidly dissolving polymer. The valve system was successfully integrated into a complex pesticide assay. By using this method, it is possible to generate time-controlled sequential release of reagents in simple and low cost paper-based devices, which is a key advantage to obtain complex assays in resource limited settings.

Rivas and his co-workers proposed a new and simple strategy of introducing hydrophobic barriers fabricated by wax printing in order to increase the sensitivity of lateral flow paper-based assays. This concept was employed for the detection of human IgG as model protein in a gold nanoparticle-based lateral flow assay.[100] The strategy proved to be compatible with any type of lateral flow assay design and convenient in POC applications.

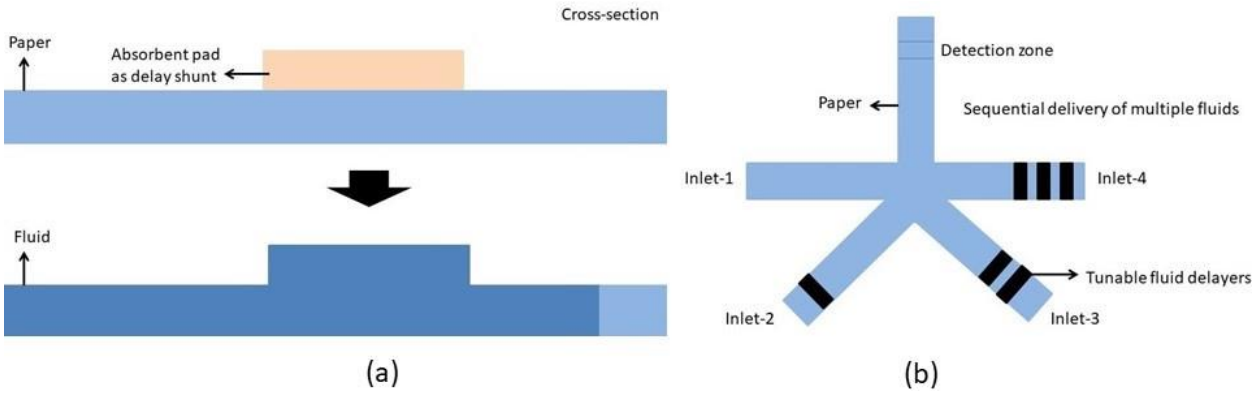


Figure 6: (a) Paper device with an absorbent pad on top. The rate of fluid flow through the paper can be altered by placing a shunt made of an absorbent material in contact with the main channel, which produces a delay in the fluid flow.[100] (b) Scheme of a paper device with multi-step fluidic programming. Each fluid is delivered to a detection zone in a timed sequence due to the fluidic time delayers.[98]

Akyazi *et al*.[54,101] manipulated fluid flow in paper by introducing two different set of ionogels materials as passive pumps in µPADs, Figure 7. It was demonstrated that ionogels highly affected the fluid flow by delaying the flow from the inlet during the sample delivery. Niedl and his co-workers demonstrated thermally activated release of samples into the paper substrate from hydrogels that served as fluid reservoirs. The material does not release liquid at room temperature, but it is able to release it when temperature is increased. Then the team integrated the technology in an antibody-based *E. coli* paper test carrying out a multi-step sequence of chemical reactions. [102] Weit *et al*.[103] used a target-responsive hydrogel as flow regulator, in order to achieve simultaneous fluidic flow and signal readout in a paper-based point of-care assay the detection of multiple targets. Rapid qualitative detection of cocaine, adenosine, and Pb^{2+} in urine within the hydrogel integrated system was carried out.

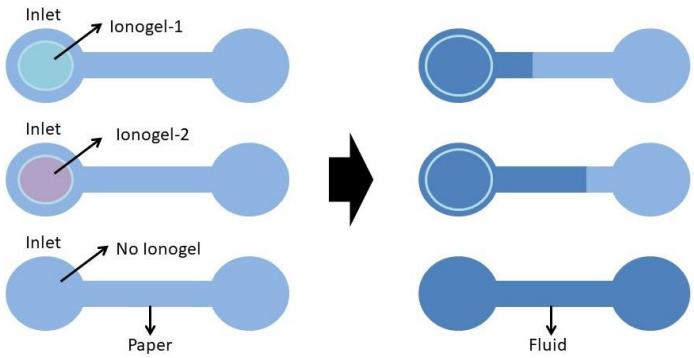


Figure 7: Performance of two type of ionogels, with different chemical and physical properties drop-casted at the inlet of a paper device. The ionogels presented different levels of fluid delay and leaded to distinctive liquid flow profiles, when compared to the bared paper.[54]

Li *et al*.[104] proposed a new kind of paper-based magnetic valve, which provides time regulated fluid control by switching on or off the flow in µPADs magnetically. This particular design reduces the complexity of the analytical tests with the possibility of multi-step operation on paper-based devices.

Noh and Philips[105] built the first fluidic timer for time-dependent POC 3D paper assays, based on the wicking time of the sample. Changes in wicking rate altered the timer in relation to the type of assay, thus allowing quantitative results. The same team also developed wax-based meters on 3D µPADs to control the movement of capillary-driven flows with precise time delays. This precise control is useful for paper-based POC assays with multiple steps, in which each step demands the interaction of the reagents for a defined period of time on the same device channel. [106] Later, Giokas *et al.*[107] demonstrated that programming fluid transport within paper-based devices is possible by cutting the main channels and generating minor channels either longitudinal or perpendicular to the flow direction with a craft-cutting tool. In order to control the acceleration or delay of flow, number, length and the orientation of open channels were customised. This

method was successfully applied to μPADs for multiple and time-programmable assays for metal ion determination.

Recently, fluidic control methods for automatic sequential delivery in 3D paper-based microfluidic devices are based on mechanically actuated valves to connect or disconnect channels.[90] Toley *et al.*[108] developed a toolkit containing automatic paper microfluidic valves using movable paper-based channels and fluid-activated swelling components. The valve actuation time was controlled by altering the lengths of the timing wicks. They demonstrated the use of these valves in a device able to perform a multi-step assay for the detection of malaria proteins. In another similar study, the control of fluid flows in a 2D paper-based device was possible by a "fluidic diode" which was a two-terminal component that favoured or prevented wicking along the paper-based microfluidic channel.[109] These technologies allow sequential analysis possible in μPADs; however the fabrication of these type of devices is time consuming and not simple to implement for mass production.

Although a lot of improvements have been recently achieved in fluid control there are significant limitations for accurate control of fluid transport kinetics when using commercially available filter papers. Therefore, Böhm and his co-workers developed a different approach towards the control and modulation of the fluid flow inside microfluidic paper channels, by using modified lab-engineered-paper sheets. Compared with commercially available papers, these lab-engineered-papers enable control over the paper composition and porosity by tuning the fibre density and therefore prevent potential side effects caused by chemical paper additives. The capillary driven transport of aqueous solutions was monitored and investigated with different fibers (*e.g.* eucalyptus sulfate and cotton linters pulp), different porosities and channel widths.[90] Janga *et al.*[110] achieved flow rate control by altering the permeability of chromatography paper using a

wax printer. Accurate control of the flow rate on paper was achieved by tuning the amount of printed wax. Salentijn *et al.*[111] developed a non-mechanical on/off valve system on paper-based on selective permeability. He showed that the level of hydrophobicity can be controlled through AKD deposition in the paper and hydrophilic behavior in the paper can be modified by oxygen plasma treatment. Consequently, the AKD deposition was used to generate valves that were impermeable to aqueous solutions but became permeable and totally wet with the addition of alcohol to the solution. Songok *et al.*[112] introduced another non-mechanical flow control method which benefits the surface energy contrast to cause a flow delay. The surface energy difference along a channel was accomplished by varying the UV exposure time of TiO_2 coated paper. They additionally demonstrated that the channel geometries provide control over flow rate and enables longer duration flows. This method eliminate the need of integration of external mechanical components just by modifying the paper hydrophobicity. Despite of having an advantage of being simple and low cost, these methods are not capable of providing an exact, time dependent delay and/or fluid control.

Sealing and enclosing of the μPADs considerably improves the device capabilities. It protects the channels and reagents from contamination by isolating them from the external environment; it simplifies the handling of the device and eliminates the need for packaging, which would reduce the final cost of the device. Moreover, it can be considered as an effective flow control method since it improves the flow capability of the device by slowing down the evaporation of the solvents and increasing the wicking rate of fluids in channels, which directly enhances the accuracy and efficiency of the device. For instance, Schilling *et al.*[113] introduced an effective and low cost method for the sealing of the top and bottom sides of the fluidic channels using the toner of a laser printer whereas Renault *et al*.[114] generated fully enclosed channels by wax printing using no

sealing. Both of the processes resulted in successful devices with improved capabilities. Other example is the work published by Kubota and his team [115] that developed a new, simple and low cost strategy to be used for both sealing process and controlling the flow in µPADs using charged surfaces by triboelectric effect. This flow control method does not change the format/shape of the hydrophilic channel nor the porous structure of paper and can be used for both delaying or accelerating the fluid transport.

In conclusion, reported fluid control systems generally fail because are included in devices with complicated fabrication and operation protocols. Additionally, these sophisticated fluid control solutions are generally considered of highly cost. The major advantages of µPADs over conventional microfluidic devices are their ability to reach to the end user thanks to their low cost and easy operation. Only considering those premises, µPADs would achieve their aim of being available even at resource-limited countries.

4. Detection in paper-based microfluidics.

There are several reviews in literature which focused on detection technologies applied to µPADs.[3,70,116] Here the most recent detection mechanisms in µPADs are briefly summarised and compared, considering their implications in commercialisation.

Detection is an important challenge in the context of POC µPADs, which includes minimising the sensing equipment for conducting the assay, generate portable devices and detection methods at low cost and ensure ease operation even by none specialised personnel. A large variety of methods have been used for the detection of analytes in µPADs, among them colorimetric detection, electrochemical (EC) sensing, fluorescence, chemiluminescence (CL) sensing and electrochemiluminescence (ECL) sensing are the most common ones. Other methods used in a less

extend like mass spectroscopy and surface-enhanced raman spectroscopy are also available in literature but will not be explained in this review.

Colorimetric sensing on µPADs is surely the most prevalent since paper substrate offers a bright, high-contrast, colourless background for colour change readings.[6,116,117] Colorimetric detection is typically related to an enzymatic or a colour-change chemical reaction where, the analysis of the results can be visually evaluated by naked eye (yes/no answer) or in a semi-quantitative way. Moreover, the method can be quantified by a calibration chart, a handheld reader, or a camera phone.[3,116] Early examples of colorimetric sensing in µPADs were demonstrated using pH, glucose and protein assays in artificial urine.[16,37] Nowadays, the pregnancy test uses a paper-based microfluidic device and a colorimetric detection technique in a simple, fast, stable, reproducible and cheap manner. The need for this type of test, and the social impact generated after its successful commercialization makes this technology unique over other detection methods. The technology came in a perfect timing and caused a revolution, being a continuous need from generation to generation.

Nevertheless, the judgment of the final colour with the naked eye is challenging due to the inhomogeneity of the colour distribution on the paper assay.[37] In addition, colorimetric sensors are normally influenced by the background noise of the paper or the sample, achieving not very low detection limits with low selectivity and sensitivity. Despite all these drawbacks, colorimetric sensing has been the most adopted sensing mechanism for µPADs, because it provides easy read-out of the generated chemical signals and enables instrument-free measurements.[3,70] Colorimetric sensing was successfully used for the detection of glucose, proteins and other biomolecules,[103,118-133] for the detection of enzymes and their inhibitors,[134-142] for the detection of metal particulates,[143-152] and bacteria,[153-157] for the agglutination or separation

of red blood as a pre-treatment process of blood samples,[40,158-161] and for immunoassays.[103,162-171]

It is clear, considering all these publications, that the complexity on the colorimetric detection of real samples is very high. Therefore, for the successful commercialisation of colorimetric µPADs, more improvements are needed on the sample manipulation, isolation of the desired molecule to be detected and on the elimination of cross-contaminants coming from the sample in the µPADs. Moreover, from the technological point of view, improvements on "cellphone technology" such as lightweight, portability, inexpensive information technology equipment for detection, software for image analysis, equipment-free readouts, stabilisation of the lighting conditions during imaging, colorimetric signal, minimisation of the effect of temperature and humidity on color, and the shelf life of the device are key factor to reach the market.[172]

Electrochemical sensing has become one of the most extensively investigated detection techniques in µPADs,[70] being glucose sensing one the most successful outputs in this field. Commercially available electrochemical glucose meters use paper based strips with screen printed electrodes or metal oxide semiconductors among others, directly printed on the paper surface. The wicking property of paper is used to move the sample (*e.g.* blood, urine) adequately towards the sensor and getting a precise signal in a short time.

In contrast to colorimetric sensing, demonstrated fast sensor responses, higher sensitivity and selectivity, enabling the detection and quantification of analytes even in the nanomolar range.[67,68,70] Additionally, the main advantage of electrochemistry, unlike colorimetry, is that it is generally insensitive to lighting conditions and contaminants (suspended solids, coloured materials) present in the samples,[173] leading to more stable signals. Moreover, the high roughness and porosity of paper substrates result in an increased surface area of the deposited

materials that improve the response of the electrochemical sensor.[174] Nevertheless, this structure can also be a disadvantage when it comes to the physical attachment of the electrodes in paper, which is sometimes hard to control.[175] Moreover in methods where the electrode is consumed during measurement, a modest amount of electrode material can result in a short lifetime of the device.[176] Electrochemical sensing was successfully used for the detection of biomolecules such as glucose, uric acid, lactate and cholesterol,[80,173,177-185] neurotransmitters and drugs,[186-194] DNA and nucleosides,[195,196], metals,[197-200] and ions,[201-204] gaseous samples,[174-176], pH change,[205,206] and immunoassays.[207-218]. Therefore, all these publications demonstrate the high potential of this detection technique, being glucose sensor devices a successful commercialisation story. Nevertheless, electrochemical sensing is open to further miniaturisation (enabling accommodation of higher density of detectors), to improved sensitivities and to faster responses. In particular, for in-field use, it is necessary to develop powerful and at the same time, portable electrochemical devices, which are key factors for the successful commercialisation of electrochemical-based μPADs. Despite of the attractive features of electrochemical detection such as maturity, miniaturisation possibilities and low levels of interference from paper, the need for a detection instrument increases the complexity and the cost per test which is a significant drawback for POC devices.[3] At the same time, the future for this field lies in basically combining sample pre-treatment and self-pumping for fluid transport, with the power of electrochemistry in μPADs.[219]

Fluorescence sensing is based on the measurement of the intensity of light emitted by a substance that has previously absorbed light or other electromagnetic radiation. In μPADs, this method often faces with some difficulties since commercially available paper substrates contain additives that

also self-fluoresce and cause high background noise.[70] Nevertheless many paper-based fluorescence sensors have been developed and have achieved low limits of detection.[6] In general, μPADs with fluorescence sensors were used for studying bacteria growth,[220] detecting bacteria,[221] proteins,[18,30,222-224] DNA,[225-227] cancer cells,[167] drugs,[228] others, [229,230] and for immunoassays.[231] Overall, fluorescence sensing provides new capabilities to μPADs, nevertheless the usefulness of fluorescence sensing will be dependent on the advances in cost reduction and miniaturisation of fluorescence readers.[3]

Chemiluminescence sensing has been considered as a sensitive and efficient analytical technique for μPADs. The method stands out for its simplicity, high sensitivity and compatibility with micromachining technologies which leads to wide dynamic range of applications even by untrained personnel.[71] Nevertheless, the measurement need to be performed in the dark which complicates device fabrication.[6] Also, this method is in need of portable chemiluminescence readers. For instance, a portable CMOS-based chemiluminescence reader was used and successfully applied in a chemiluminescence immunoassay (CLIA) by a company called Anitoa. [232] This CMOS-based solution is capable of detecting as low as a few ng mL^{-1} of analyte, such as proteins. Therefore, although portable CL readers are available in the market but their cost is relatively high since this is a newly introduced technology. A positive thing is the reduced background noise, since it does not require an external light source, which is an advantage compared to the fluorescence method.[71] In μPADs, this sensing method was adopted for biomolecules detection (for uric acid, glucose and hormones),[233-235] measuring DNA hybridisation,[236] DNA detection,[237,238] cancer detection,[239]

immunoassays,[13,139,240,241] metal detection,[242] and in pesticide detection from food products.[243]

Electrochemiluminescence sensing mechanisms are based on generating luminescence by electrochemical reactions. Electrochemically generated intermediates result in an electronically excited state whenever they undergo exergonic reactions. When molecules are in this state, enable readouts without the need of a photo-detector, as they emit light while they relax to a lower level state. The most outstanding feature of electrochemiluminescence sensing is its applicability in both, luminescence and electrochemical detection methods. Electrochemiluminescence has also some advantages over chemiluminescence such as lower background, ability to control reagent generation and improved selectivity via potential control.[3,70] Some remarkable μPADs with electrochemiluminescense sensing were used for the detection of biomolecules,[58,244,245] cancer cells,[246] ions and metals,[247] chemical contaminants,[248] and immunoassays, mainly for tumour marker detection.[249-252] In this detection technique, readouts must be conducted in the dark, since the detection is ambient-light-dependent and requires a power source which is costly to be miniaturise. Due to these drawbacks, it is not a sensing method for resource-limited conditions at the moment and not applicable in commercial systems.[3]

In conclusion, considering both qualitative and quantitative sensing strategies, paper microfluidics technology is mainly facing low sensitivity and poor accuracy.[253] Improving the sensitivity of the μPADs is possible by either adding new steps to the mentioned detection techniques which could cause increase in complexity and cost of the device or by preferably developing/adopting innovative detection methods that both simplify the device and increase efficiency at the same

time. This will assure that µPADs could reach the market faster and with higher standards of quality.

5. Applications of Paper-based Microfluidic Devices

As it has been highlighted in previous sections it can be concluded that the main application of µPADs is to provide to the users a portable, low cost, easy to use analytical platform for diagnostic assays.[68] Only low cost diagnostic assays can be manufactured in large volumes and be affordable by the end-users. Thus, monitoring and controlling diseases and environmental contaminations all around the world, even in resource limited countries, it would be only possible by delivering simple, cheap and robust diagnostic tests. From this point of view, µPADs can be seen as the most convenient alternative to conventional devices in the developing world.

The current applications of µPADs can be categorised into three groups as summarised in Table 3.

Table 3: µPAD applications.

Health diagnostics	Analysis of biomolecules such as proteins, hormones, neurotransmitters, *etc*.	[5,103,119,124,130,131,139,142, 164,179,186,188,189,210,223, 245,248,254,255]
	Analysis of small molecules such as glucose, uric acid, *etc*.	[52,53,74,123,125,129,185,233, 234,256-260]
	Nucleic acid analysis.	[195,196,221,225-227,236,238, 261-265]

	Immunoassays for infectious diseases and cancer detection.	[140,154,162,163,166-168, 170,193,208,212-214,217, 220,231,237,239,240,241,250, 266-273]
	Pregnancy tests	[274]
	Blood typing and blood filtering	[158-161,275]
	Drug sensing.	[135,138,187,192,228,235,276]
Environmental diagnostics	Water, soil, air analysis, metal detection *etc*.	[136,143-145,148-152,157,199, 200,244,247,248,277-284]
Food and Beverage Control	Pesticide, foodborne, *etc*. detection, water and wine quality analysis, *etc*.	[134,147,243,285-287]

It is clear that research in medical diagnostic is focusing significant amount of efforts on paper-based microfluidic devices due to their critical importance and high commercial perspectives. For instance, the commercialisation of paper-based pregnancy tests, which are one of the first lateral flow assays, was considered as one of the major breakthrough in this field.[288] But it was more recently, when µPADs were re-introduced as real alternatives to generate low cost and disposable biochemical sensing devices for multiple applications.[16]

µPADs are of critical importance since they enable POC detection and can ideally be used massively in low income countries, where people predominantly die of preventable or curable infectious diseases: lower respiratory infections, HIV/AIDS, diarrheal diseases, malaria and tuberculosis collectively, accounting for almost one third of all deaths in these countries. While significant progresses have been made in interventions to prevent and treat most of these diseases, often the effort are not widely reaching all population due to the lack of laboratory infrastructure, trained personnel and financial support.[28,253,289,290] Therefore, affordable, equipment free, simple to operate, and robust diagnostic assays at the point of care would be considered as life savers under these resource-limited conditions.[291-293] The aim of µPADs for POC is to obtain the results quicker in order to take clinical decisions instantly and to carry out the treatment plan immediately.[294] Moreover µPADs fulfil the World Health Organisation (WHO) **ASSURED** criteria for an ideal rapid test: **A**ffordable, **S**ensitive, **S**pecific, **U**ser-friendly, **R**apid and robust, **E**quipment free, **D**eliverable to end users, delivering affordable POC diagnostic tests.[253]

Moreover, µPADs are of considerable social and commercial importance in the developed world. People in these countries live longer; older people who lead to highest expenditures in both public and private health systems are reshaping the healthcare market. For instance, in public health systems, as a result of the difficulty of recovering the high costs related with drug treatments of elderly population, restrictions on drugs use are being considered. Moreover, pharmaceutical companies are demanded to prove that their products are effective in decreasing the symptoms beyond the boundaries of controlled clinical trials environments, therefore big efforts are needed for the development of novel companion diagnostics test at a low cost.[295] Additionally, early diagnosis of diseases like cancer, where the detection and sometimes quantification of molecules and biomolecules like glucose, lactate, uric acid, alcohol, biomarkers for liver function, ATP, ALT,

nitrite, nucleic acids among others is needed in physiological fluids like blood and urine, can be successfully accomplished by µPADs.

The potential of µPADs is not only limited to healthcare; devices developed for environmental safety, detecting water, soil or air contamination, and for food and beverage control are also available at the laboratory state. In the resource-limited countries or after a natural disaster like an earthquake, to be able to determine drinking water quality with an easy to use and low cost paper-based device would be very beneficial. Furthermore, the possibility of controlling the quality of foods and beverages by the final consumer and ensuring the control over the whole food/beverage production chain would be an important advantage for farmers, production companies and sellers in order to generate a more dynamic market,[292] and it is also necessary for public health to prevent diseases such as the ones transmitted by faecal-oral route through nutrients. Therefore it is here where µPADs are realistic alternatives for low cost, mass production and marketable devices.

Finally it is worthy to mention that veterinary diagnostics is another area compatible with µPADs since affects human health by human-animal contact, food, animal transportation and in clothing.[3]

6. Conclusion

Microfluidics has been gaining maturity as reflected in both, the growing number and the improved quality of articles published on this topic. Even though significant progresses are continuously appearing in microfluidics, some serious obstacles are still facing the development of sample-in/answer-out microfluidic systems, especially in the areas of sample preparation, chip to real world interfacing, detection and miniaturisation or elimination of external fluidic control elements.

Due to the complexity and high cost of these developments, the amount of commercial products based on microfluidics remains low, having difficulties to meet with the end-users.

New µPADs fabrication protocols are progressing to meet the end-users/marketing requirements; therefore, paper is fulfilling the ideal platform material criteria for the transition of this technology from laboratory to the market. As a result of the excellent properties of paper, µPADs are developed as an answer to provide simple and low cost microfluidic devices easily manageable by the end-users, which enable useful analytical platforms to be used in a wide range of applications. These applications are increasing day by day due to the improved capabilities of µPADs in sample preparation, fluid control, detection and miniaturisation.

The transition of paper-based microfluidic devices from the laboratory into the users´ hands will be fully achieved by providing an effective fluid flow control on paper. The recent development in this area are real success stories, nevertheless they lack of a rapid and easy way of manufacturing and industrial implementation. Therefore, developing simple and low-cost µPADs with integrated flow control methods which are applicable in existing mass production and fabrication facilities will reach to a successful commercialisation of these type of devices.

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